Effects of Co-Occurring Depression on Treatment for Anxiety Disorders: Analysis of Outcomes From a Large Primary Care Effectiveness Trial

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ABSTRACT

Objective: Co-occurring depression is common in patients seeking treatment for anxiety; however, the literature on the effects of depression on anxiety treatment outcomes is inconclusive. The current study evaluated prescriptive and prognostic effects of depression on anxiety treatment outcomes in a large primary care sample.

Method: Data were analyzed from a randomized controlled effectiveness trial that compared coordinated anxiety learning and management (CALM) to usual care. The study enrolled 1,004 patients between June 2006 and April 2008. Patients were referred by their primary care provider and met *DSM-IV* criteria for generalized anxiety disorder, panic disorder, posttraumatic stress disorder, and/or social anxiety disorder. They were treated for approximately 3 to 12 months with CALM (computer-assisted cognitive-behavioral therapy, medication management, or their combination) or usual care. Outcomes were evaluated by blinded assessment at 6, 12, and 18 months. Effects of baseline major depressive disorder (MDD) on anxiety symptoms, anxiety-related disability, and response/remission rates were evaluated using statistical models accounting for baseline anxiety and patient demographics.

Results: MDD did not moderate the effects of CALM (relative to usual care) on anxiety symptoms, anxiety-related disability, or response/remission rates. Greater improvements in anxiety symptoms and anxiety-related disability were observed in depressed patients, regardless of treatment assignment (*P* values < .005). However, cross-sectionally depressed patients displayed higher anxiety symptom and anxiety-related disability scores at baseline and all subsequent assessments (*P* values < .001). Depressed patients also displayed lower remission rates at each follow-up (*P* values < .001).

Conclusions: CALM had comparable advantages over usual care for patients with and without MDD. Depressed patients displayed more severe anxiety symptoms and anxiety-related disability at baseline, but their clinical improvement was substantial and larger in magnitude than that observed in the nondepressed patients. Results support the use of empirically supported interventions for anxiety disorders in patients with co-occurring depression.

Trial Registration: ClinicalTrials.gov identifier: NCT00347269

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Epidemiologic studies[1,2] report high comorbidity rates among anxiety and mood disorders in the general population, and co-occurrence of these disorders is even higher in treatment-seeking samples.[3,4] Patients with principal anxiety disorders who also meet criteria for a mood disorder have more severe anxiety symptoms, impairment, and course than those without co-occurring mood disorders.[5] Understanding the effects of co-occurring depression on treatment for anxiety disorders is important, particularly if effects are discovered that have implications for treatment selection or implementation.

The available literature does not permit strong conclusions about the influence of depression on anxiety treatment outcomes. Most studies have considered depression as a potential predictor or prognostic indicator of outcome (ie, a variable that demonstrates a relationship to outcome variables irrespective of treatment assignment).[6] Results of these studies have been mixed; some[7–11] observed that co-occurring depression predicted reduced improvement of anxiety symptoms, while others[12–18] found no significant effects of depression on degree of clinical improvement. Lack of consistent findings may be attributable to a variety of factors from heterogeneous patient samples, study interventions, and assessment measures to statistical issues related to small sample sizes.

Randomized controlled trials of anxiety interventions have rarely evaluated depression as a potential moderator or prescriptive indicator of outcome (ie, a variable that interacts with treatment assignment and affects outcome differentially across groups).[19] Studies to date that have included this type of analysis have reported no significant prescriptive effects of depression on anxiety outcomes.[20,21] However, additional work (preferably with larger samples) is needed before conclusions about the prescriptive effects of depression can be drawn.

In the present investigation, we aimed to clarify the effects of depression on anxiety treatment outcomes by analyzing data from a large sample (N > 1,000) of primary care patients with anxiety disorders who received treatment as part of the Coordinated Anxiety Learning and Management (CALM) study. The CALM intervention is superior to usual care in reducing anxiety symptoms and anxiety-related disability (and in producing clinical response and remission) during 18 months of follow-up.[4,22] However, it is unknown whether these effects are moderated by co-occurring depression.

On the basis of the available literature, we hypothesized that (1) depressed patients would display more severe anxiety symptoms and anxiety-related disability at baseline; (2) depressed patients would display more severe anxiety

Clinical Points

- Depression is common in patients seeking treatment for anxiety disorders, and depressed patients often present with more severe anxiety symptoms and other clinical complexities.
- Depression does not, however, compromise the effectiveness of standard treatments for anxiety disorders; on the contrary, substantial reductions in anxiety symptoms and disability were observed in depressed patients receiving treatment for anxiety disorders.
- Empirically supported treatments for anxiety (cognitive-behavioral therapy, medication management, or their combination) should typically be offered to patients with co-occurring depression.

symptoms and anxiety-related disability at follow-ups (prognostic effects); and (3) despite its expected association with increased anxiety severity, depression would not moderate the effects of the CALM intervention on anxiety symptoms and anxiety-related disability, ie, co-occurring depression would not be a prescriptive indicator of outcome.

METHOD

Participants

Participants were patients enrolled in the CALM study (ClinicalTrials.gov identifier: NCT00347269), a randomized controlled trial conducted in 17 primary care clinics located in Seattle, Washington; Los Angeles, California; San Diego, California; and Little Rock, Arkansas. Patients provided informed consent to participate, and the study was approved by institutional review boards at all study sites. Patients were referred to the study by their primary care providers; in some clinics, referral was facilitated by a 5-item anxiety screener.[23]

Between June 2006 and April 2008, 1,004 patients with *DSM-IV* anxiety disorders (panic disorder, generalized anxiety disorder [GAD], posttraumatic stress disorder [PTSD], and/or social anxiety disorder), aged 18 to 75 years, English or Spanish speaking, were enrolled in the study. Most co-occurring disorders, including MDD, were permitted; active suicidal intent or plan, psychosis, bipolar I, and substance use disorders (except for alcohol and marijuana abuse) were cause for exclusion. Table 1 presents the demographic and diagnostic characteristics of the sample.

Design of the CALM Study

Prior reports[4,24] have provided detailed descriptions of the CALM study design. Briefly, eligible participants were randomly assigned to CALM or usual care; randomization was stratified by clinic and presence/absence of MDD. Stratification, therefore, ensured equivalent assignment of participants with MDD to CALM and usual care. Blinded telephone assessments were performed by the RAND Survey Research Group at baseline, 6, 12, and 18 months. Study retention was high and similar for the CALM and usual care groups, with more than 80% of participants assessed at each follow-up.

Intervention. Patients assigned to usual care received care as usual from their primary care physician, with no restrictions imposed (eg, patients could receive pharmacotherapy, in-house counseling if available, or be referred out for specialty care). Patients assigned to CALM met with an anxiety clinical specialist and were given the choice of computer-assisted cognitive-behavioral therapy (CBT), medication management, or both. The majority of patients selected CBT, either as monotherapy or in combination with medication.[4]

The CALM algorithm allowed for multiple treatment steps over the course of the 12-month period. The patient's preferred treatment (CBT, medication management, or both) was delivered as the initial step over a period of 10–12 weeks. If needed, the patient could receive up to 3 additional treatment steps before the 12 months elapsed, which could include either "stepping up" by adding more of the same modality (eg, providing CBT sessions focused on a secondary anxiety disorder; adding a second antidepressant or a benzodiazepine to first-line pharmacotherapy) or "stepping over" by switching to or adding the other modality. Once patients had achieved criteria for remission[4] or improved to the degree at which they did not want further treatment, they entered a relapse prevention phase during which they received monthly phone calls to reinforce CBT skills, medication adherence, or both, until the 12-month treatment period had elapsed. Prior reports provide additional details of the CALM intervention[4,24,25] and anxiety clinical specialist training.[26]

Measures

Depression. Major depressive disorder (*DSM-IV* criteria) and other diagnoses were established by using the Mini-International Neuropsychiatric Interview (MINI), version 5.0.[27] Reliability and validity of MDD diagnoses established with the MINI are satisfactory.[27] The MINI was conducted in person by the anxiety clinical specialist at the participant's primary care clinic. Depressive symptoms also were measured during the baseline telephone assessment by using items from the Patient Health Questionnaire-9, a reliable and valid measure of depressive symptoms.[28]

Anxiety symptoms. The primary outcome of the CALM study was the sum of the anxiety and somatization subscales of the well-validated Brief Symptom Inventory.[29] This subset of 12 items (the 12-item Brief Symptom Inventory [BSI-12]) captures psychic and somatic anxiety, which characterize all anxiety disorders.[4]

Anxiety-related disability. Disability was measured by using the well-validated Sheehan Disability Scale,[30] which measures the degree to which symptoms disrupt work/school, social functioning, and family/home life. For the CALM study, the instructions that preceded each of the ratings were modified to target anxiety-related disability (eg, "Anxiety, tension, and worry symptoms have disrupted your work/schoolwork . . .").

Table 1. Baseline Patient Characteristics[a]

Characteristic	All (N = 1,004)	No Major Depressive Disorder (n = 356)	With Major Depressive Disorder (n = 648)
Age, mean (SD), y	43.47 (13.44)	42.25 (13.67)	44.15 (13.28)
Women	714 (71.12)	239 (67.14)	475 (73.30)
Education			
< High school	55 (5.49)	9 (2.53)	46 (7.12)
12 y	165 (16.47)	44 (12.36)	121 (18.73)
> 12 y	782 (78.04)	303 (85.11)	479 (74.15)
Ethnicity			
Hispanic	196 (19.52)	63 (17.70)	133 (20.53)
African American	116 (11.55)	26 (7.30)	90 (13.89)
White	568 (56.57)	223 (62.64)	345 (53.24)
Other	124 (12.35)	44 (12.36)	80 (12.35)
No. of chronic medical conditions			
0	202 (20.14)	88 (24.72)	114 (17.62)
1	219 (21.83)	92 (25.84)	127 (19.63)
≥ 2	582 (58.03)	176 (49.44)	406 (62.75)
Anxiety disorder[b]			
Panic	475 (47.31)	169 (47.47)	306 (47.22)
Generalized anxiety	756 (75.30)	245 (68.82)	511 (78.86)
Social phobia	405 (40.34)	125 (35.11)	280 (43.21)
Posttraumatic stress	181 (18.03)	27 (7.58)	154 (23.77)
Type of health insurance[b]			
Medicaid	101 (10.08)	23 (6.46)	78 (12.07)
Medicare	124 (12.38)	34 (9.55)	90 (13.93)
Other government insurance[c]	35 (3.49)	12 (3.37)	23 (3.56)
Private insurance	749 (74.75)	289 (81.18)	460 (71.21)
No insurance	141 (14.07)	39 (10.96)	102 (15.79)
Any opiate use	86 (8.57)	13 (3.65)	73 (11.27)
Any pain	441 (43.92)	93 (26.12)	348 (53.70)
Intervention[d]	503 (50.10)	173 (48.60)	330 (50.93)

[a]Data are reported as n (%) unless otherwise indicated.
[b]Because patients could have more than 1, *n*'s may total more than 1,004.
[c]Includes Veterans Administration benefits, TRICARE, county programs, or other government insurance not otherwise specified.
[d]Randomization to coordinated anxiety learning and management intervention (versus usual care) was stratified by presence/absence of major depressive disorder.

Response and remission. Following the main CALM outcome study, treatment response was defined as achieving a 50% or greater reduction in baseline BSI-12 score or meeting the criteria for remission.[4] Remission was defined as a BSI-12 score of 6 or less (ie, a per-item average of 0.5 or the midpoint of "none" and "mild").

Statistical Analysis/Design of the Current Study

To estimate the effect of baseline MDD over time, we jointly modeled the outcomes (BSI-12 and Sheehan Disability Scale scores) at the 4 assessment points by treatment assignment (CALM vs usual care), time (baseline, 6, 12, and 18 months), MDD (presence vs absence of MDD at baseline),* and the interaction of treatment assignment, time, and MDD. Study site, education level, gender, race/ethnicity, and age were included in all models as covariates. In models in which the 3-way (treatment assignment × time × MDD) interaction was nonsignificant, we refit the model including 2-way interactions of treatment assignment × time and MDD × time, dropping the 3-way interactions. Time was treated as a categorical variable. To avoid restrictive assumptions, the covariance of the outcomes at the 4 assessment points was left unstructured.

We fitted the proposed model by using a restricted maximum likelihood approach, which produces valid estimates under the missing-at-random assumption.[31] This approach correctly handles the additional uncertainty arising from missing data and uses all available data to obtain unbiased estimates for model parameters.[32] This is an efficient way to conduct intent-to-treat analyses, as it includes all participants with a baseline assessment.

For cross-sectional analyses involving response and remission rates, we used attrition weights to correctly account for participants who missed 1 or more follow-ups.[33]

The statistical software used was SAS version 9 (SAS Institute Inc, Cary, North Carolina). All *P* values were 2-tailed and a conservative significance level of $P < .01$ was adopted to account for multiple comparisons.

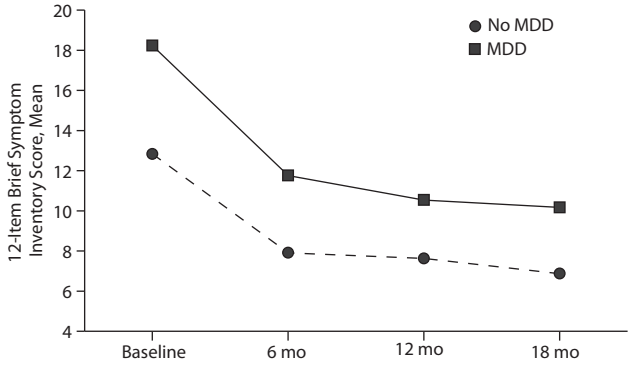
*Analyses were repeated by using baseline scores on the items from the Patient Health Questionnaire-9 in place of MDD diagnostic status. The same pattern of results was obtained, suggesting that the effects of depression reported here are robust to differences in construct definition (categorical vs dimensional) and mode of assessment (clinician-administered vs self-report). Results of the analyses using the Patient Health Questionnaire-9 items are available upon request.

RESULTS

Demographic and Diagnostic Differences Related to MDD

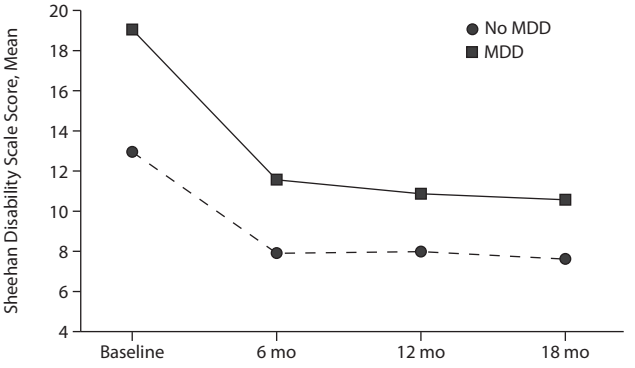
Table 1 summarizes the demographic and diagnostic characteristics of participants with and without MDD. Nearly

Figure 1. Predicted Mean 12-Item Brief Symptom Inventory[a] Score at Baseline, 6 Months, 12 Months, and 18 Months by Major Depressive Disorder (MDD) Status[b]



[a]Includes the anxiety and somatization subscales of the Brief Symptom Inventory.
[b]Improvement (relative to baseline) was greater in the MDD group than in the non-MDD group at 12 months ($P<.001$) and at 18 months ($P=.002$). However, the absolute scores were higher in the MDD group than in the non-MDD group at baseline and all follow-up assessment points (P values $<.001$).

Figure 2. Predicted Mean Sheehan Disability Scale[a] Score at Baseline, 6 Months, 12 Months, and 18 Months by Major Depressive Disorder (MDD) Status[b]



[a]Modified to capture disability related to anxiety.
[b]Improvement (relative to baseline) was greater in the MDD group than in the non-MDD group at 6, 12, and18 months (P values $<.001$). However, the absolute scores were higher in the MDD group than in the non-MDD group at baseline and all follow-up assessment points (P values $<.001$).

two-thirds (64.5%) of the sample met criteria for MDD at baseline. The group with MDD had higher proportions of Hispanic and African American participants and a lower proportion of white participants ($P=.005$). Those with MDD also reported lower educational levels ($P<.001$) and more chronic medical conditions ($P<.001$), pain ($P<.001$), and opiate use ($P<.001$). They were more likely to have Medicaid ($P=.005$) and less likely to have private insurance ($P=.001$). Greater proportions of participants with MDD met criteria for GAD ($P<.001$) and PTSD ($P<.001$).

Effects of MDD on Anxiety Symptoms

The treatment assignment × time × MDD effect on BSI-12 scores was nonsignificant ($P=.555$), indicating that baseline MDD did not moderate the effects of CALM on anxiety symptoms. Two-way interactions were then examined, revealing a significant MDD × time effect on BSI-12 scores ($F_{3,991}=5.08$, $P=.002$). Depressed participants displayed larger decreases than nondepressed participants in anxiety symptoms, regardless of treatment assignment (Figure 1). While the group difference was not significant at $P<.01$ at 6 months (mean difference = −1.40, standard error [SE] = 0.60; $t_{991}=-2.35$, $P=.019$), a significant difference was observed at 12 months (mean difference = −2.34, SE = 0.62; $t_{991}=-3.79$, $P<.001$) and 18 months (mean difference = −1.96, SE = 0.63; $t_{991}=-3.11$, $P=.002$). A main effect of MDD also was observed in which BSI-12 scores were higher for patients with baseline MDD, regardless of time or treatment assignment (mean difference = 5.25, SE = 0.57; $t_{991}=9.22$, $P<.001$; see Figure 1).

Effects of MDD on Anxiety-Related Disability

The treatment assignment × time × MDD effect on Sheehan Disability Scale scores was nonsignificant ($P=.524$), indicating that baseline MDD did not moderate the effects of CALM on anxiety-related disability. Two-way interactions were then examined, revealing a significant MDD × time interaction ($F_{3,991}=10.99$, $P<.001$). Depressed participants displayed larger decreases in anxiety-related disability, regardless of treatment assignment (Figure 2). This was observed at 6 months (mean difference = −2.26, SE = 0.56; $t_{991}=-4.02$, $P<.001$), 12 months (mean difference = −3.03, SE = 0.56; $t_{991}=-5.39$, $P<.001$), and 18 months (mean difference = −2.96, SE = 0.60; $t_{991}=-4.93$, $P<.001$). A main effect of MDD also was observed in which disability was higher for participants with baseline MDD, regardless of time or treatment assignment (mean difference = 5.91, SE = 0.45; $t_{991}=13.25$, $P<.001$; see Figure 2).

Effects of MDD on Response and Remission

Table 2 presents response and remission rates for depressed and nondepressed patients assigned to CALM and usual care. The within-group comparisons displayed in Table 2 show that, for depressed patients, CALM was superior to usual care in producing clinical response and remission at all follow-up points.

There were no significant treatment assignment × MDD interaction effects on response rates at 6, 12, or 18 months (P values $>.14$). A main effect of MDD was observed at 6 months ($P=.009$), in which participants with MDD displayed a lower response rate (44%; 95% CI, 39%–48%) than those without MDD (53%; 95% CI, 47%–59%). However, between-groups differences did not meet the threshold for significance at 12 months ($P=.144$) or 18 months ($P=.025$).

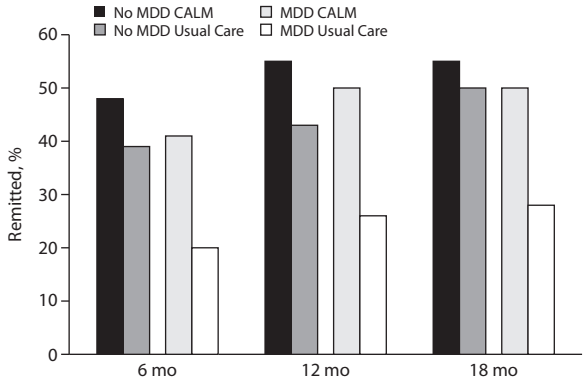
Major depressive disorder × treatment assignment interaction effects also were nonsignificant for remission at 6 months ($P=.038$), 12 months ($P=.094$), and 18 months ($P=.015$). Although not significant at $P<.01$, it is noteworthy that, at 6 months, twice the percentage of depressed patients receiving CALM (41%) achieved remission compared to

Table 2. Proportion Achieving Response and Remission From Baseline 12-Item Brief Symptom Inventory Score[a,b]

	MDD at Baseline			No MDD at Baseline		
	CALM, Proportion (95% CI)	Usual Care, Proportion (95% CI)	*P* Value	CALM, Proportion (95% CI)	Usual Care, Proportion (95% CI)	*P* Value
Response[c]						
6 mo	0.56 (0.50–0.61)	0.32 (0.26–0.38)	< .001	0.62 (0.54–0.69)	0.44 (0.37–0.52)	.002
12 mo	0.63 (0.57–0.69)	0.41 (0.35–0.47)	< .001	0.66 (0.57–0.73)	0.50 (0.42–0.58)	.009
18 mo	0.64 (0.58–0.70)	0.46 (0.40–0.52)	< .001	0.67 (0.59–0.75)	0.60 (0.52–0.68)	.236
Remission[d]						
6 mo	0.41 (0.35–0.47)	0.20 (0.15–0.25)	< .001	0.48 (0.41–0.56)	0.39 (0.31–0.47)	.087
12 mo	0.50 (0.44–0.56)	0.26 (0.21–0.32)	< .001	0.55 (0.47–0.63)	0.43 (0.35–0.51)	.040
18 mo	0.50 (0.43–0.56)	0.28 (0.22–0.34)	< .001	0.55 (0.46–0.63)	0.50 (0.42–0.58)	.421

[a]Data presented as proportion weighted for nonresponse at each follow-up.
[b]12-Item Brief Symptom Inventory includes the anxiety and somatization subscales of the Brief Symptom Inventory.
[c]*Response* defined as ≥ 50% reduction on the 12-Item Brief Symptom Inventory, with all those in remission considered to have responded.
[d]*Remission* defined as a per item 12-Item Brief Symptom Inventory score of < 0.5 (total score < 6).
Abbreviations: CALM = coordinated anxiety learning and management, MDD = major depressive disorder.

Figure 3. Proportion Remitted at 6 Months, 12 Months, and 18 Months by Baseline MDD Status and Treatment Assignment



Abbreviations: CALM = coordinated anxiety learning and management, MDD = major depressive disorder.

those receiving usual care (20% remission, or a 21% advantage for CALM; Table 2 and Figure 3). The difference in 6-month remission rates for CALM versus usual care was less pronounced for the nondepressed group (48% vs 39%, or a 9% advantage for CALM). This pattern also was apparent at 12 and 18 months (see Table 2 and Figure 3). Main effects of MDD on remission rates were observed at all 3 assessment points (*P* values < .003), with remission rates being lower for participants with MDD.

DISCUSSION

Co-occurring depression was common in this sample of primary care patients with anxiety disorders, with nearly two-thirds of patients meeting criteria for MDD at baseline. This comorbidity rate is consistent with the extensive literature showing a strong association between anxiety and mood disorders, particularly in clinical samples.[5] Depressed participants had higher rates of GAD, PTSD, and medical comorbidity than nondepressed participants and endorsed more severe anxiety symptoms and anxiety-related disability at baseline. Regarding sociodemographic characteristics, participants with co-occurring MDD were more likely to identify as Hispanic and African-American, to endorse a low educational level, and to qualify for Medicaid. These baseline findings suggest that primary care patients with co-occurring anxiety disorders and MDD often present with additional clinical complexities (eg, co-occurring medical problems, social challenges related to lower education/financial resources) that may play a role in their anxiety and mood symptoms.

Despite the more severe and complex baseline presentation of depressed participants, co-occurring MDD did not significantly moderate the effects of the CALM intervention (relative to usual care) on anxiety symptoms, anxiety-related disability, or treatment response and remission rates. This finding converges with results of prior studies with smaller samples showing no prescriptive effects of depression on treatment outcomes following behavioral treatment for anxiety disorders.[7,8]

In contrast, co-occurring MDD was prognostic of outcomes over the 18 months of follow-up, predicting both magnitude of improvement and absolute levels of anxiety symptoms and anxiety-related disability at each assessment point. Irrespective of treatment assignment, depressed participants improved more yet still appeared worse than nondepressed participants at all follow-up assessments. The higher absolute levels of symptoms and disability (and hence lower remission rates) in the depressed group appeared to be a by-product of their baseline elevations, which were not fully compensated for by their larger improvements on the anxiety outcome measures.

The analyses of remission rates merit comment, as the results were striking yet not significant at the a priori threshold of *P* < .01. For depressed patients, the 6-month remission rate in CALM was twice that of usual care (41% versus 20%). The corresponding difference in the nondepressed group was less dramatic (48% versus 39%). This pattern persisted at subsequent follow-ups, and it is noteworthy that, at the final assessment (18 months), depressed patients who received usual care displayed particularly low remission rates (28%)

compared to all other patients (50%–55%; see Table 2 and Figure 3). These data suggest that usual care may have particularly low efficacy for patients with co-occurring depression, whereas higher-intensity interventions such as CALM may improve likelihood of remission in this subgroup.

Clinical Implications

As noted in previous reports,[4,22] the CALM intervention is superior to usual care in reducing anxiety symptoms and anxiety-related disability in primary care patients with anxiety disorders. The current findings support the use of CALM and similar empirically supported interventions for anxiety disorders in patients with co-occurring depression. The lack of moderation of the CALM intervention effect by MDD suggests that, contrary to some clinical opinion, the potency of empirically supported treatments for anxiety is not generally compromised by co-occurring depression. On the contrary, improvements in anxiety symptoms and anxiety-related disability associated with CALM and usual care were larger for the depressed versus the nondepressed participants. These improvements were not only statistically but clinically significant; collapsing across CALM and usual care, the average anxiety symptom score for depressed participants was in the "mild" range at all follow-up assessments.

Factors Contributing to the Effect of Depression on Degree of Clinical Improvement

To our knowledge, co-occurring depression has not been associated with larger improvements in previous studies examining prognostic effects of depression on anxiety treatment outcomes. Prior studies have found either less clinical improvement[10–14] or equivalent degrees of change[15–21] in depressed patients relative to comparison groups. We therefore considered potential factors that may have contributed to this discrepant finding.

First, the more naturalistic design of CALM (compared to efficacy trials) may partly explain the larger improvements observed in the depressed participants. Rather than prescribing a set number of sessions, the CALM intervention allowed clinicians and patients to work flexibly toward a goal of clinical remission. Primary care providers and any specialist clinicians who treated patients assigned to usual care were presumably working toward a similar goal. Within this context, it is not entirely surprising that depressed participants displayed greater clinical change; because they started with more severe symptoms, larger decreases would be required for them to approach the goal of remission. Study clinicians had a range of options available for targeting the symptoms of patients with more complicated presentations, including "stepping up" by adding more of the initial treatment modality or "stepping over" to the alternative treatment modality.

To investigate this further, we conducted post hoc analyses to explore whether the more severe initial presentations of depressed participants prompted clinicians to deliver treatment differently. For patients assigned to CALM, data were available from the study's Web-based tracking system (see Supplementary eTable 1). We found that depressed and nondepressed patients assigned to CALM did not differ significantly in terms of proportions who received CBT only, medication management only, and combination treatment. There also were no significant between-group differences in the total number of in-person, telephone, active treatment, or relapse prevention visits with study clinicians. However, a significant difference was found in the number of visits coded as medication management visits, with depressed patients receiving approximately 1 more visit of this type on average compared to nondepressed patients. The only other difference that approached statistical significance ($P = .013$) was in the direction of nondepressed patients receiving more CBT contacts; on average, they received approximately 1 more CBT contact than depressed patients.

For the full sample, data were limited to patients' self-reports of treatment from the baseline and 6-, 12-, and 18-month assessments. Rates of depressed and nondepressed patients who reported receiving key elements of CBT during treatment sessions did not differ significantly at any of the follow-ups. Not surprisingly, depressed participants were more likely to report using antidepressant or antianxiety medication of adequate type, length, and dose (see Stein et al[34] for the study's operational definitions of adequate pharmacotherapy); however, the advantage that depressed patients had on this indicator of treatment quality was greatest at baseline (33.0% vs 23.7%) and decreased thereafter, becoming nonsignificant by the final follow-up point (41.3% vs 34.8%). While clear implications cannot be deduced from this pattern, it is possible that the difference in rate of adequate pharmacotherapy, the greater number of visits focused on medication management (as observed in the CALM group), or other aspects of medication treatment (eg, more aggressive regimens) could have contributed to the larger improvements observed in the depressed group.

In addition to differences in treatment delivery, patient factors influencing outcome should also be considered as a potential explanation for the larger improvements in depressed patients. It is possible that participants who were more impaired at baseline (as the depressed participants were) may have been more motivated to comply with treatment recommendations than those whose symptoms were less disabling. Again, this type of effect could be more apparent in an effectiveness study conducted in a real-world setting than in an efficacy trial conducted in a research setting (where there may be less variability in treatment adherence due to more stringent controls in subject selection and treatment delivery).

Finally, and importantly, it may have been more difficult to demonstrate change in the nondepressed participants because they endorsed relatively low anxiety symptom and anxiety-related disability scores at baseline. Conversely, the more severe baseline symptoms and disability of the depressed patients may have allowed more room for improvement on the outcome measures. This basic measurement issue could have contributed to the different magnitudes of improvement observed in the depressed and nondepressed groups.

Limitations

The current study elucidates the effects of depression on treatment for anxiety in a mixed anxiety disorder sample. Due to statistical power considerations, the study was not designed to evaluate further interactions involving specific anxiety disorder diagnoses (ie, 4-way interactions among principal anxiety diagnosis, MDD, treatment assignment, and time). The results reported here cannot be assumed to apply uniformly to each individual anxiety disorder.

In addition, the CALM study evaluated a multifaceted intervention involving CBT, medication management, or their combination. Our results pertain specifically to the effects of depression on the CALM package compared to usual care. Design considerations preclude us from drawing conclusions regarding the influence of depression on the effectiveness of specific components of CALM. While participants were randomly assigned to CALM or usual care, the components of CALM they received (CBT, medication management) were not randomly assigned but dictated by patient and provider choice. Future investigations should evaluate potential prescriptive effects of depression on the specific modalities of CBT and pharmacotherapy, as this could aid in selection of an optimal empirically supported intervention for anxiety.

Conclusions and Future Directions

Co-occurring depression did not moderate the effects of CALM on anxiety symptoms, anxiety-related disability, or response/remission rates. Improvements in anxiety symptoms and anxiety-related disability were clearly demonstrated for depressed participants. These results support the use of interventions such as CALM for patients with co-occurring depression, especially when considered in conjunction with findings that depressive symptoms often improve with effective treatment of anxiety disorders.[4,35] Clinicians implementing such interventions in primary care settings can expect higher absolute levels of anxiety-related symptoms and disability (as well as additional complexities such as medical comorbidity and challenges related to social conditions) in depressed patients relative to nondepressed patients referred for similar interventions. However, the magnitude of improvement also may be greater for the depressed patients. Some noteworthy findings that did not meet the a priori threshold for statistical significance suggested the possibility of a stronger advantage of CALM over usual care in producing remission of anxiety symptoms in the depressed participants. Future research should continue to explore the issue of whether higher-intensity interventions such as CALM are even more strongly indicated in anxiety patients with more complicated initial presentations involving co-occurring depression.

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Potential conflicts of interest: **Dr Roy-Byrne** is a consultant to and stock shareholder in Valant Medical Solutions (EMR Company) and is Editor-in-Chief of *Journal Watch Psychiatry*, *Depression and Anxiety*, and *UpToDate Psychiatry*. **Dr Stein** has received grant/research support from the National Institute of Mental Health and is Co-Editor-in-Chief for *UpToDate Psychiatry*. **Drs Campbell-Sills, Sherbourne, Craske, Sullivan, Bystritsky, Lang, Chavira, Rose,** and **Welch** have no disclosures.
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Supplementary Material

Article Title: Effects of Co-Occurring Depression on Treatment for Anxiety Disorders: Analysis of Outcomes From a Large Primary Care Effectiveness Trial

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List of Supplementary Material for the article

1. eTable 1 Characteristics of Treatment Received by Depressed and Non-Depressed Patients Assigned to CALM
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This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1.

Characteristics of Treatment Received by Depressed and Non-Depressed Patients Assigned to CALM

	MDD (n = 312)	No MDD (n = 170)	*p* value
Modalities Received			
CBT Only	108 (34.6%)	58 (34.1%)	.100, *ns*
MM Only	34 (10.9%)	9 (5.3%)	
CBT + MM	170 (54.5%)	103 (60.6%)	
In-person visits with ACS	8.69 (4.70)	9.28 (4.32)	.178, *ns*
Phone visits with ACS	4.33 (4.45)	4.04 (3.50)	.419, *ns*
CBT visits with ACS	6.69 (4.20)	7.64 (3.83)	.013*
MM visits with ACS	2.64 (4.12)	1.49 (2.01)	.000**
Active treatment visits with ACS	9.34 (5.11)	9.12 (4.10)	.603, *ns*
Relapse prevention visits with ACS	3.72 (3.49)	4.18 (3.45)	.162, *ns*

Note. Data presented are from the 482 patients (out of 503 randomized to CALM) who had at least one intervention contact with the ACS.
CALM = Coordinated Anxiety Learning and Management; MDD = Major Depressive Disorder; CBT = Cognitive-Behavioral Therapy, MM = Medication Management, ACS = Anxiety Clinical Specialist.
*Significant at $p < .05$; note that this does not meet this study's *a priori* threshold for statistical significance ($p < .01$).
**Significant at $p < .001$.